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Review

Expanding the Criteria for Heart Transplantation Donors: A Review of DCD, Increased Ischemic Times, HCV, HIV, and Extended Criteria Donors

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Abstract

With the demand for heart transplantation continuing to outpace the available donor organs, previously underutilized donors are now being reconsidered. We sought to describe the emerging techniques and outcomes of expanded criteria heart transplantation. A comprehensive review of the recent literature concerning expanded donor selection in heart transplantation was performed using the PubMed MEDLINE database. To characterize trends in transplant practice, the United Network for Organ Sharing (UNOS/OPTN) registry was queried for all adult isolated heart transplants since 2010, and data regarding transplant parameters was collected. Donation after cardiac death (DCD), DCD with normothermic regional perfusion, increased ischemic time, hepatitis C positive donor organs, HIV-positive donor organs, and extended criteria donors were identified as promising avenues currently being explored to expand the number of donor organs. The utilization of various expanded criteria for heart transplantation was summarized since 2010 and showed an increasing use of these donor organs, contributing to the overall increasing frequency of heart transplantation. Utilization of expanded criteria for donor selection in heart transplantation has the potential to increase the supply of donor organs with comparable outcomes in selected recipients.

Keywords

heart transplantation; donor criteria; donation after cardiac death (DCD); ischemic time; normothermic regional perfusion; HCV+ transplantation; HIV+ transplantation

Introduction

When Dr. Christiaan Barnard performed the first successful heart transplant (HT) at Cape Town's Groote Schuur Hospital in December of 1967, the world was taken by storm [1]. Centers around the globe jumped to replicate the operation, and 102 heart transplants were completed worldwide in the next year [2]. However, Barnard's first recipient, a 54-year-old man with end-stage ischemic cardiomyopathy, survived only 18 days post-transplant. The outcomes of these surgeries across the world were similarly grim, leading to a significant curtailment of HT [2]. Today, with over 50 years of HT experience and the advent of effective immunosuppression [2], outcomes have significantly improved. Recipients have a median survival of greater than 12 years [3] and HT has become the definitive treatment for patients with end-stage heart failure.

However, the number of candidates awaiting HT worldwide has continued to rise, driven by significant advancements in the care for patients with advanced heart failure, including advancements in optimal medical therapy, cardiac resynchronization therapy, transcatheter and open interventions as well as ventricular assist devices (VAD) [4]. The discrepancy between waitlisted candidates and available organs exists in regions across the world, with an average of 15–30% of European transplant candidates dying on waitlists [5]. In other regions, including South America, Africa, and Asia, heart transplantation is expanding, resulting in a growing need for donor organs [6,7].

This growing demand has caused the transplant community to seek ways to expand the donor pool, resulting in a 65% increase in United States donor hearts since 2009 [4]. Some of this increase has been due to the re-evaluation of donor hearts that would previously have been discarded, as use of those allografts for HT might still confer an advantage over remaining on the waitlist. In this study, we review the major categories of previously underutilized donors that have received recent reconsideration and which have the potential to reduce the disparity between supply and demand for heart allografts (Fig. 1) (Ref. [9,17–19,28–31,35,38,39,51–53,56–62,84–96,100–103,105–109,114,116,117,121,127,131,134,136–138,140–153]).

	Advantages	Disadvantages
DCD NRP NMP	✓ Comparable outcomes to traditional DBD adult recipients [9,17-19] ✓ NRP has been well established for abdominal organ procurement [28-30] ✓ With allograft perfusion, NRP permits longer transport times [35,38,39] ✓ NMP may support longer preservation times and achieve higher organ usage ✓ Strict policies and separation of donor and procurement teams may mitigate ethical controversy [51-53]	× Unavoidable warm ischemic time [9] × Difficulty in assessing function of asystolic donor heart [9] × NRP is not as well characterized in thoracic organ procurement [31] × Ethical concerns regarding circulatory death, determining irreversibility, informed consent, and withdrawal of life support [51-53]
Increased Ischemic Time	✓ Improves flexibility of threshold for time between procurement and implantation ✓ Strategies, such as *ex vivo* perfusion and hypothermic oxygenation perfusion, show promise ✓ Early studies with both strategies suggest comparable outcomes to traditional methods [84-94]	× Associated with worse outcomes in kidney, liver, lung, and heart transplantation [56-60] × Morbidity and mortality risk increases with older recipients with more comorbidities × Potential risk of allograft fibrosis and left ventricular stiffness [61,62]
HCV	✓ HCV D+/R- transplantation successful with comparable outcomes, even long-term [100-103,109] ✓ HCV seroconversion can be treated with DAAs [91] ✓ No difference in rates of rejection, hospitalization, dialysis, stroke, retransplantation, renal impairment with HCV D+ organs [105-107, 114] ✓ Early studies successful in pediatric population [108] ✓ ~200 successful HCV D+ transplants across 60 centers in the United States [109]	× DAA treatment and insurance approval may implicate administrative burden × Risk of transmission of HCV in HCV- recipients [95,96] × HCV associated with increased coronary allograft vasculopathy [95,96] × Potential harmful interaction between DAA treatment and immunosuppressants [157]
HIV	✓ Increases access to donor organs for HIV+ recipients, who are transplanted at lower rates ✓ HIV D+/R+ transplantation successfully demonstrated in liver and kidney recipients ✓ Efficacy of HAART has improved management and decreases chances of transmission [116,117] ✓ Single case report showed no HIV-related complications, rejection, or abnormal biventricular function [121]	× Not well established, limited to one case report [121] × Increased risk of acute organ rejection in HIV D-/R+ transplantation [127] × Risk of transmission of HIV if recipient is HIV-, including new strains × Potential interaction between HAART treatment and immunosuppressants [131]
Extended Criteria Donors	✓ Older donor age hearts offer survival benefit to status IA and >60 years old recipients [140,142] ✓ Confirmed via angiography, donor CAD hearts showed no difference in outcomes [144-146] ✓ Donor organs with left ventricular hypertrophy or decreased donor ejection fraction can be successful with comparable outcomes [147-153]	× Historically, associated with higher mortality and morbidity [134] × Increased donor age associated with increased risk of cardiac allograft vasculopathy [136-138,141] × Using donor hearts with CAD often requires back table cardiac bypass grafting [143] × Conflicting data regarding ECD utilization when donor has other comorbidities [151-153]

Fig. 1. Summary of advantages and disadvantages for different approaches to expanding heart transplantation. Extended criteria donors include increased ischemic time (listed separately), advanced age, history of coronary artery disease, and decreased ejection fraction. DCD, donation after circulatory death; NRP, normothermic regional perfusion; NMP, normothermic machine perfusion; DBD, donation after brain death; HCV, hepatitis C virus; D, donor; R, recipient; DAA, direct acting antiviral; HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy; CAD, coronary artery disease; ECD, extended criteria donors.

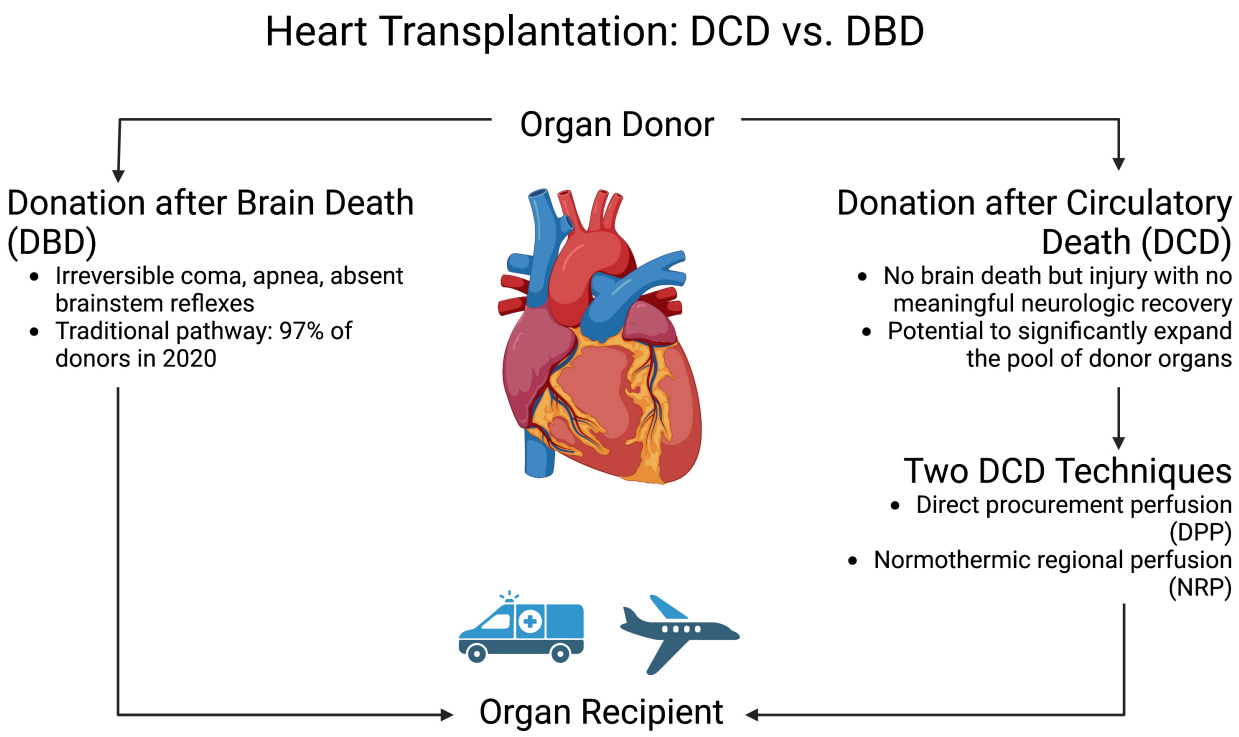

Fig. 2. Comparison of Donation after Circulatory Death (DCD) *vs.* Traditional Donation after Brain Death (DBD) in Heart Transplantation. Created with BioRender.com.

Donation after Circulatory Death (DCD)

While the groundbreaking original HT performed by Barnard occurred before the legal definitions of organ transplantation had been codified, today it would be considered to be a donation after circulatory death (DCD) transplant [1,8,9]. First conceptualized in the 1960's, brain death was codified by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research as the Uniform Determination of Death Act in 1981 [10,11]. A widely-used definition of brain death was proposed by the American Academy of Neurology in 1995 and updated in 2010, stipulating that irreversible brain death was indicated by the clinical findings of apnea, irreversible coma, and the absence of brain stem reflexes [11]. In contrast, DCD occurs when donors are not classified as brain dead but nonetheless have severe brain injuries with no prospect of meaningful recovery (Fig. 2) [9,12]. DCD donation then only proceeds after donors meet the criteria of death due to irreversible cardiopulmonary arrest after withdrawal of life support [12].

Donation after brain death (DBD) donors have been long preferred in HT and represented 97% of donor organs used in the United States in 2020 [4,9]. The discrepancy in the numbers of DCD and DBD HT exists largely because transplant teams must grapple with two intrinsic challenges of DCD: the unavoidable warm ischemic time for the organ and the difficulty in assessing function of the asystolic donor heart before transplantation [9]. The "functional-warm ischemic injury" period begins when the heart is not perfused or oxygenated adequately after life support is withdrawn and concludes when the heart is either flushed (in the direct procurement technique) or re-perfused with normothermic regional perfusion (NRP), which will be detailed further in the following section [12].

In the past two decades, despite these inherent challenges, the decreasing number of DBD donors and the increasing utilization of DCD in abdominal transplants has reinvigorated investigation into DCD donors in HT [9]. The first modern report of DCD HT was published in 2008 by Boucek *et al.* [13] and described 3 infants who underwent DCD HT with equivalent 3-year survival and functional outcomes as matched DBD controls. However, there were significant questions surrounding the protocol of this investigation, as Boucek *et al.* [13] shortened the required duration of asystole to 75 seconds from 5 minutes [14,15]. Excitement over the results of Boucek *et al.* [13] was tempered by a multicenter retrospective analysis of 21 pediatric DCD HT from 2005 to 2014 which showed markedly lower 1-year survival among recipients of DCD *vs.* DBD HT (61% *vs.* 91%), despite more DBD recipients requiring bridging to HT with ECMO [16].

Despite these findings of inferior outcomes from DCD HT in small studies of pediatric patients, groups in Australia and the United Kingdom have worked to expand DCD HT in recent years and published promising results [15]. Both Chew *et al.* [17], reporting results of the Aus-

Table 1. Techniques and Short-Term Outcomes of Selected DCD Transplantation Experiences.

	Chew *et al*. [17]	Messer *et al*. [18]	Madan *et al*. [12]
Study Population	Australian experience at St. Vincent's Hospital (2014–2018)	UK experience at Royal Papworth Hospital (2015–2020)	United States experience (2020)
DCD Method	DPP	DPP, NRP	DPP, NRP
Number of DCD transplants	23	79	136
30-day survival (%)	95%	97%	96.8%*
1-year survival (%)	95%	91%	

*Kaplan-Meier estimate.

tralian team, and Messer *et al*. [18], reporting from the UK, demonstrated survival outcomes among adult DCD recipients comparable to DBD recipients. However, there were substantial rates of graft dysfunction in both cohorts, with high utilization of mechanical support and ECMO post-transplant [9,17–19]. Significantly, 5-year results from the Australian group were published in 2020, showing 5-year survival of 94% in a cohort of 32 DCD heart transplants. However, of 49 donor organs retrieved, 17 were ultimately declined for transplantation because of rising lactate levels demonstrating myocardial injury. These results show both the promise of DCD as well as the remaining questions about optimizing *ex-situ* perfusion [20].

In 2022, Madan and colleagues published the American experience, with DCD HT recipients showing no difference in 1- or 6-month mortality or secondary outcomes including length of stay compared to contemporary adult DBD recipients [12]. These results affirmed the promise of DCD HT while emphasizing the need for long-term follow-up data on these patients (Table 1) (Ref. [12,17,18]). Further studies are needed to evaluate longer-term outcomes, including 5- and 10-year survival.

Despite the increasing interest in DCD HT, Madan *et al*. [12] also reported that only 136 of the 3611 DCD donors (3.8%) referred from January 2020 to February 2021 in the United States were used for HT [21]. If even a small percentage of these discarded organs are suitable for HT, DCD organs have the potential to substantially increase the supply of heart allografts. Madan *et al*. [12] estimate that widespread utilization of DCD HT across the United States could lead to approximately 300 more HT per year. In the UK, Messer *et al*. [22] anticipated that even with strict guidelines for organ selection, national HT volume could increase by 56% with broader DCD implementation. In Asia, the lack of brain death legislation in many countries has led to a novel technique known as donation after brain death followed by circulatory death (DBCB), which has helped to assuage some ethical and religious concerns and could increase donor supply [23]. Therefore, considering recent findings of equivalent outcomes for DCD *vs.* DBD HT and estimates suggesting vast underutilization of DCD donor organs, transplant providers should strongly consider DCD organ offers to increase waitlist candidates' access to transplant without compromising outcomes.

Use of DCD with NRP

During DCD procurements, organs can either be directly procured or an attempt can be made to improve organ preservation and function using normothermic regional perfusion (NRP). As utilization of DCD organs has increased, so, too, has interest in using NRP for potentially marginal organs to increase the number of DCD organs deemed suitable for transplant [19,24–26]. NRP uses veno-arterial extracorporeal membrane oxygenation (VA-ECMO) to perfuse allografts after pronouncement of circulatory death, with the goal of allowing the heart to recover from the associated warm ischemic injury [27]. NRP is well established and characterized in abdominal organ procurement but has not been widely adopted in heart procurement [28–30], with only 95 (1.5%) of all HT in the US from 2019–2021 performed with NRP [31].

Thoracoabdominal NRP (TA-NRP) is used for thoracic organs including the heart and lungs. TA-NRP involves the cannulation of the right ventricle and aorta. The arch vessels are clamped to prevent antegrade cerebral blood flow. After approximately one hour of TA-NRP, the heart and/or lungs are reevaluated and—if deemed suitable for use—procured, and static cold storage or machine perfusion is used during organ transport [32–35].

Preliminary studies of TA-NRP DCD for HT in both large animal models [35,36] and humans [35–47] have shown patient and allograft survival not statistically different from that of DBD. In most cases, TA-NRP is followed by cold static storage. While the literature on TA-NRP HT includes numerous case reports [36,43–47], in recent years, there have been a growing number of single-center studies of TA-NRP HT with up to 28 patients [35,37–42]. These studies have shown that TA-NRP enabled longer transport times, including a peak cold ischemic time of 201 minutes, while maintaining a 100% survival rate at 30 days post-transplant [35,38,39,46]. Case reports of TA-NRP use in pediatric patients have also shown promising 30-day patient and allograft survival [48,49]. Overall, the small body of existing evidence for TA-NRP for DCD HT supports continued use and evaluation of this technique.

Utilization of NRP for DCD HT is expected to grow in coming years. Thus far, however, despite literature doc-

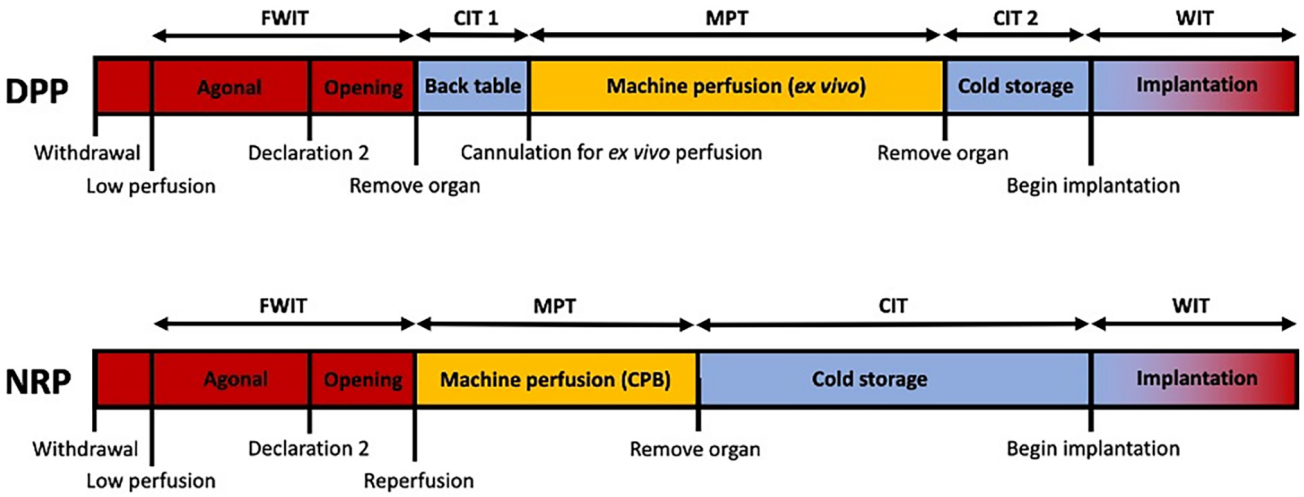

Fig. 3. Direct Procurement and Perfusion (DPP) *vs.* Normothermic Regional Perfusion (NRP). In both approaches, care is withdrawn and the donor reaches an agonal (hypoxic [oxygenation <70%] and hypotensive [<50 mmHg systolic blood pressure]) state. In DPP, the organ is removed and perfused in an *ex vivo* device. In NRP, the body (excluding cerebral flow) is perfused with cardiopulmonary bypass (CPB). FWIT, functional warm ischemic time; CIT, cold ischemic time; MPT, machine perfusion time; WIT, warm ischemic time.

umenting the safety of NRP, its adoption has progressed relatively slowly in the cardiac field due to significant ethical and quality concerns. In a 2020 survey of Canadian providers by Honarmand *et al*. [50], 92.3% found DCD with direct procurement and perfusion acceptable, while only 78.4% found DCD with TA-NRP acceptable; the study posited ethical concerns, resource availability, allograft quality, and impact on other organs as reasons for provider hesitance to use or increase use of TA-NRP. DCD with NRP highlights many of the same ethical issues seen in DCD, namely that perfusion is being resumed in a body that underwent supposedly "irreversible" circulatory death. However, Parent *et al*. [51] and others suggest DCD with TA-NRP can be performed ethically with strict policies that prioritize donor life and informed consent, specifically not discussing DCD until an uncoerced decision to withdraw life support is made, making sure the decision to consent to DCD is fully informed, and maintaining separation between the donor's clinical team and the procurement team [52,53].

Literature describing the logistics of implementation is also increasing, reflecting increased openness and standardization to TA-NRP [32–34]. These procedural descriptions include instructions for anesthesia, echocardiography, and heart function measurement, providing a guide for centers interested in incorporating NRP into their procurements [35,54,55]. With concerns about TA-NRP in DCD HT being addressed and accessibility increasing with standardized procedures, utilization of DCD HT with TA-NRP provides a promising means of increasing the donor pool for HT.

Increased Ischemic Times

Ischemic time (IT) is minimized in solid organ transplantation to maximize preservation of allograft function. Increased ischemic time has been associated with worse outcomes in kidney and liver transplant [56,57], and in lung transplant an upper limit of six hours is often used for ischemic time [58–60]. In HT, mechanistic studies have shown increased allograft fibrosis [61] and left ventricular stiffness [62] associated with increased IT. However, the role of IT in survival, as a risk factor, and for complications varies between studies.

Post-HT survival among recipients of allografts with longer IT has been reported to be inferior or similar to that of recipients of allografts with shorter IT, depending on the study. Multiple studies report no difference in survival by IT [63–68]. However, more recent studies report an increase in mortality after 4 hours IT [69,70], with Yeen *et al*. [71] finding no difference in survival for less than 4 hours IT *vs.* 4–5 hours IT but a decrease in survival with IT greater than 5 hours.

Unique patient risk factors may contribute to the variable association of ischemic time with survival. The negative impact of IT on recipient survival appears to increase with age [69,72–74], and Novick *et al*. [58] identified an interaction between donor age and IT. Other factors, including recipient ECMO, dialysis, and ischemic etiology of heart failure have been reported to increase the risk of IT on survival. This data emphasizes the potential risks of using increased ischemic time donors, especially in recipients with known risk factors. In contrast, left ventricular ejection fraction above 65% and donor obesity have been re-

ported to be protective against increased IT [75–77]. Until the exact mechanisms underlying these differences are elucidated, transplant providers can use the presence of these risk factors to guide risk estimation and counseling when considering IT and HT survival.

Like survival, the association of increased IT on post-transplant complications has been reported as both neutral and negative. While early studies observed no association between IT and 90-day graft loss, sinus node dysfunction, and coronary artery disease [64,78,79], in later studies increased IT was found to be associated with graft loss, early rejection, and decreased post-transplant exercise capacity [80–82], as well as increased cost [67,83].

Ex vivo perfusion is one approach proposed to address potential adverse effects of prolonged IT. *Ex vivo* perfusion, or direct procurement and perfusion (DPP) involves removing the heart before perfusion, compared to NRP, which perfuses the heart while still in the body (Fig. 3). *Ex vivo* perfusion is in its early stages for use in HT, but preliminary results in both animal and human studies show *ex vivo* perfusion can support increased IT without significant differences in survival [84–89]. In the future, *ex vivo* perfusion may be used to help mitigate the risks associated with increased IT, allowing for prolonged allograft preservation.

Hypothermic oxygenated perfusion is another method to preserve heart function, especially for prolonged transport times, by addressing the concern of inconsistent organ cooling in traditional icebox storage. SherpaPak™ Cardiac Transport System (CTS) (Paragonix Technologies, Cambridge, MA, USA) aims to maintain organ temperature at 4–8 °C, with the goal to preserve function and prevent protein denaturation. Animal studies have shown this device enables improved cell structure preservation and temperature maintenance as compared to traditional cold storage [90–92]. Small-scale human studies have shown the device to have similar outcomes to traditional cold storage in infection rates, graft failure, and hemodynamic parameters, all while maintaining temperatures between 4–8 °C [93,94]. Thus, the SherpaPak™ CTS may be a valuable tool, especially in grafts with increased ischemic time.

In summary, longer IT has been associated with greater morbidity and mortality, particularly among older and sicker patients. Therefore, the preferred recipients for allografts with longer IT might be waitlisted candidates that are younger and healthier. Advances in *ex vivo* perfusion and hypothermic oxygenated perfusion may help mitigate the risks associated with increased IT and make increased IT allografts a more appealing option to increase the HT donor pool.

Hepatitis C Positive Donor Organs

Hepatitis C (HCV) is a viral infection that typically manifests with liver inflammation and, over time, irreversible scarring and organ damage. HCV spreads through contact with contaminated blood, resulting in an estimated 66,000 new infections annually in the United States. HCV infection is determined by serological testing and nucleic acid amplification testing (NAAT). HCV donor organs can be classified as either antibody seropositive without viremia (Ab+ NAAT–), which often reflects a resolved HCV infection, or viremic with NAAT positivity (NAAT+), reflecting active viral replication. Historically, HCV+ organs have been transplanted into HCV+ recipients, but the use of these organs for HCV– recipients was not allowed due to concerns about viral transmission, particularly with NAAT+ donor organs, as well as an association with HCV+ HT and coronary allograft vasculopathy [95,96].

Due to the opioid epidemic, the prevalence of HCV among potential organ donors has been increasing over the past decade [96,97]. Additionally, HCV can now be cured with direct-acting antiviral agents (DAAs) [96]. This concurrent increase in the number of HCV-positive (HCV+) donor organs available and ability to cure HCV infection has broadened the pool of potential recipients of HCV+ organs to include HCV– waitlist candidates.

The first successful cardiac transplant with a HCV NAAT+ donor heart in a HCV– recipient was carried out at Baylor University Medical Center in 2017 [98]. Donor-derived HCV transmission occurred with the viremic organ, but the recipient's HCV viremia was promptly resolved after DAA treatment with sofosbuvir/velpatasvir [98]. With Schlendorf *et al.* [99] publishing a case series with similar success shortly afterwards and a constantly growing demand for donor hearts, HCV D+/R– transplantation began to be adopted across the United States and continued to demonstrate comparable outcomes to transplants employing HCV-seronegative donors. However, HCV+ donor organs remain underutilized in HCV negative (HCV–) recipients.

There have been an array of case reports and academic investigations aiming to characterize morbidity and mortality outcomes with HCV D+/R– transplantation. Repeated studies have demonstrated that upon HCV D+/R– HT using NAAT+ donor organs, recipients undergo seroconversion and are successfully treated with various DAA regimens without adverse impact on short-term outcomes [100–103]. In an extension of their initial case series, Schlendorf *et al.* [104] found that recipients of NAAT+ donor organs demonstrated a survival rate of 90.4% after 1 year, which was similar to that of recipients of HCV– donor organs as well as recipients with Ab+ NAAT– donor organs.

Corroborating these findings, further studies have reported that the use of HCV NAAT+ donor hearts in HCV D+/R– HT yielded no differences in the rates of organ rejection with and without drug treatment, hospitalization, post-operative dialysis, stroke, and re-transplantation in addition to mortality [105–107]. Although limited to a small sample, HCV D+/R– transplantation using Ab+ NAAT– donor or-

gans has even been carried out in pediatric patients without any significant effect on posttransplant graft survival, consistent with the outcomes observed in adult transplantation [108]. As more data has accumulated, longer 3-year outcomes of recipients of HCV D+/R– transplants have been shown to be similar to those of recipients of HCV D–/R– transplants using national registry data, even when accounting for pretransplant mechanical circulatory support (MCS) [109].

The optimal regimen and timing in transplant patients continues to evolve, especially with the advent of newer generations of DAAs. While DAAs have traditionally been given to recipients who develop viremia after transplantation, studies have shown that prophylactic use of DAA regimens successfully treat viremia without any serious adverse events post-transplant [110–113]. Timing of DAA administration in HT patients is heavily influenced by insurance approval, which can often require a prior authorization, perhaps eliciting an administrative burden that may be a barrier to use of these organs. Lastly, a common complication in cardiac transplantation is renal impairment, perhaps through increasing inflammation and perioperative hypoperfusion of the kidneys. In addition, HCV is associated with renal impairment, likely as a result of the formation of immune complexes and cryoglobulins [114]. Fortunately, it was demonstrated that neither donor-derived HCV infection nor its treatment with sofosbuvir-based DAAs was associated with an increased risk of renal dysfunction [114].

Since the first successful HCV D+/R– HT in 2015, nearly 200 additional HCV D+/R– HT have been performed across 60 different centers in the U.S. [109]. With repeated successful demonstrations and effective treatment of donor-derived HCV infection and excellent 3-year post-transplant outcomes, transplantation with HCV non-viremic (Ab+ NAT–) and viremic (NAT+) donor organs offers a means to expand access to heart transplantation.

Human Immunodeficiency Virus

Under the 1988 United States National Organ Transplant Act, people with human immunodeficiency virus (HIV) were excluded from being donors or recipients in transplantation due to concerns with increased risks of organ failure or acute rejection and accelerated HIV to Acquired Immune Deficiency Syndrome (AIDS) progression with immunosuppression [115]. However, the development of highly active antiretroviral therapy (HAART) transformed HIV into a chronic disease and dramatically improved the life expectancy of people living with HIV [116,117]. People living with HIV became candidates to receive organ transplants, but they remained barred from donating their organs.

Recently, however, transplant providers have reconsidered the use of HIV-positive (HIV+) donor organs for HIV+ recipients. HIV donor-positive to recipient-positive (D+/R+) transplantation was first demonstrated and pioneered in South Africa, where Muller *et al*. [118] conducted 27 successful HIV D+/R+ kidney transplants with excellent post-transplant survival, including 84% patient and graft survival at 3 years. Based on these data and advocacy by transplant providers, the United States signed and enacted the HIV Organ Policy Equity (HOPE) Act in 2015, which allowed for HIV D+/R+ transplantation in the United States under approved research protocols [119]. This marked a major effort to expand the donor pool for HIV+ candidates, who had traditionally been transplanted at lower rates than HIV– candidates. Additionally, transplanting HIV+ donor organs would increase the availability of HIV– donor organs for other waitlist candidates. The HOPE Act also allowed for the utilization of donor organs with false-positive HIV tests, which is estimated to occur in 50 to 100 donors annually [120].

While HIV D+/R+ transplantation has now been successfully performed for kidney and liver recipients at multiple centers, HIV D+/R+ cardiac transplantation in the United States is currently limited to a single case in 2021, as reported by Hemmige *et al*. [121]. The recipient underwent a combined heart and kidney transplant; the heart donor had recently diagnosed HIV, an undetectable viral load, and an unknown HIV treatment regimen [121]. Although the recipient had post-transplant complications including infection and an initial decline in $CD4^+$ lymphocyte counts due to transplant-related immunosuppression medications, the recipient did not have any HIV-related complications and HIV viral load remained undetectable with a treatment regimen consisting of tenofovir alafenamide, emtricitabine, and dolutegravir [121]. At 90 days post-transplant, the recipient was able to ambulate and displayed no evidence of rejection or abnormal biventricular function [121]. This case report shows promise for expanding the donor pool to improve access to transplantation for patients living with HIV and advanced heart failure.

Given the extremely limited national experience with HIV D+/R+ HT in the U.S. to date, transplant providers have learned about the management of HIV+ recipients from those receiving HIV donor-negative to recipient-positive HT (D–/R+). HIV D–/R+ HT have been documented in case reports and retrospective observational studies with promising outcomes [122–126]. In a multicenter retrospective study of 21 HIV D–/R+ HT, survival for HIV+ recipients was 90% at 1 year, 73% at 3 years, and 64% at 5 years, similar to rates observed in the overall HT recipient population [127]. As mentioned previously, one of the greatest concerns regarding HIV D–/R+ HT is acute organ rejection, which occurred in 13 of 21 (62%) recipients [127]. This high incidence of acute organ rejection has been attributed to "excessively cautious use of immunosuppression" and infrequent use of induction immunosuppression, which represents an intense, prophylactic therapy for

specifically vulnerable patients to prevent early acute rejection [127]. Nevertheless, studies using national registry data have illustrated that HIV D/R+ HT results in comparable graft and patient survival to HIV D–/R– HT [128,129]. Lastly, factors that may improve posttransplant morbidity and mortality include undetectable viral loads pretransplant, normal CD4 cell counts, and no relevant history for opportunistic infections [124].

Although transplanting Hep C+ or HIV+ organs presents an opportunity to increase the donor pool, it also carries significant risks. In 2007, 4 transplant recipients tested positive for HIV and HCV after receiving organs from one donor who had tested negative pre-transplant with routine serologic studies. Upon retest of donor samples with NAT, HIV and HCV were detected. Ultimately, two recipients died and the transplanted organs failed in two others, demonstrating the potential risks of unwitting recipient viral transmission [130]. In cases where Hep C+ or HIV+ status is known, there are also risks to the recipient, including the association of increased immunologic rejection in HIV+ recipients. Beyond that, there is a concern that superinfecting the recipient with a new HIV strain could help the virus to elude HAART therapies. Finally, it is unclear how DAA and HAART therapy may interact with the necessary immunosuppressive regimen for transplant recipients [131].

Given the success of HIV D–/R+ HT and the one successful HIV D+/R+ HT in the United States, HIV D+/R+ HT remains a promising strategy to increase access to transplant for HIV+ recipients, freeing up HIV– donor offers for other waitlist candidates. However, the impact of HIV D+/R+ transplantation on overall HT volume is limited by the number of HIV+ waitlist candidates. Additionally, given the relative novelty of the use of HIV+ organs, ongoing monitoring of short- and long-term outcomes of HIV D+/R+ transplants is needed to confirm the safety and efficacy of this procedure.

Use of "Extended Donor Pool" Hearts

Extended criteria donors (ECDs), also known as "marginal donor hearts", include those with increased ischemic time, advanced age, a history of coronary artery disease, and decreased ejection fraction [132,133]. Historically, use of organs from these donors was associated with increased morbidity and mortality compared to use of organs from standard criteria donors (SCDs) [134]. Increasingly, however, the use of ECD organs is being re-evaluated in the wake of new evidence and the continued organ shortage. In 2001, the Crystal City guidelines were proposed to maximize the use of extended criteria donors and address waitlist mortality. The guidelines stipulated the use of aggressive hormonal resuscitation and hemodynamic management to salvage previously-discarded organs [135]. In many cases, current evidence suggests that the use of ECD organs provides survival benefit to specific subpopulations of waitlist candidates.

Advanced donor age has long been associated with increased morbidity and mortality in both adult and pediatric HT [136–140]. Older donor age is associated with increased recipient mortality at 1, 5, and 15 years posttransplant, as well as a higher likelihood of developing cardiac allograft vasculopathy (CAV) [136–138,141]. In 2014, Weber *et al*. [142] established that HT using organs from donors >40 years old is associated with inferior post-HT survival. The negative impact of donor age on survival increases with donor age, with donors >55 years old being associated with the worst survival [142]. However, HT with older donor age hearts has been shown to provide a survival benefit to recipients facing imminent death (status IA) and also has similar median survival and rates of graft failure for recipients greater than 60 years old [140,142]. Overall, donor age is associated with inferior post-HT recipient survival, likely due to the increased risk of CAV. However, these grafts can still be considered for select candidate populations.

There was a paucity of literature on the use of donor hearts with coronary artery disease (CAD) until 2003, when Marelli *et al*. [143] reported on the results of 22 CAD transplants in recipients either facing imminent death (status I) or who would not have otherwise been transplanted (status II). Three of four patients with status I and 10 of 18 with status II received hearts that had coronary bypass performed on the back table. Marelli *et al*. [143] reported 1-month and 2-year survival, respectively, of 75% and 50% for status I patients and 88% and 81% for status II patients. Based on these findings, the authors recommended that donor hearts with less than mild plaque in 1 or 2 vessels could be considered for older status I recipients [143]. Recent investigation has confirmed that donor hearts with CAD can be used effectively even when coronary bypass grafting is required [144]. Finally, two studies have shown no difference in outcomes between non-CAD and CAD donor hearts. Lechiancole *et al*. [145] demonstrated that moderate CAD of a donor heart did not affect survival and did not cause accelerated development of high-grade CAV in recipients. Using the UNOS database from 1987 to 2017, Jahanyar *et al*. [146] demonstrated no difference in median, 5-, or 10-year survival between recipients of donor hearts with (n = 650, 7.5%) or without (n = 7952, 92.5%) donor CAD proven by coronary angiography. However, both studies lacked granularity on the extent of individual donor CAD and whether donor organs necessitated coronary bypass grafting [145,146]. In selected patients, using hearts with CAD may help to expand the existing donor pool, guided by the results of donor coronary angiography.

Other extended criteria for donors which have seen increased re-evaluation are decreased ejection fraction and left ventricular hypertrophy (LVH). Several studies have

Table 2. Key ethical questions for extended criteria groups in heart transplant.

Donor Type	Key Ethical Questions
Donation after Cardiac Death (DCD)	• Does restarting the heart after declaration of cardiac death revoke the "irreversible" nature of death criteria? • Does *in vivo vs. ex vivo* perfusion alter the ethics of DCD? • Does the established use of DCD in non-cardiac solid organs make DCD acceptable for heart transplant?
Normothermic Regional Perfusion (NRP)	• Does NRP attenuate concerns for DCD by maintaining brain death in the donor?
Increased Ischemic Time	• How can the use of increased ischemic time increase equity in heart transplant?
Hepatitis C	• How can be recipients best be counseled on the acceptance of Hepatitis C+ organs to achieve maximally informed consent?
Human Immunodeficiency Virus (HIV)	• How can access to cardiac transplant be increased for patients with HIV? • Does the beneficence of HIV+ transplant outweigh the potential risks?
Extended Criteria Donors	• Do the risks of transplanting hearts with increased comorbidities outweigh the potential benefits? • What role do recipients have in selecting organs based on comorbidities?

suggested that decreased donor ejection fraction does not negatively impact post-transplant mortality [147–149]. In all studies, the transient left ventricular systolic defect normalized post-transplant and was not associated with worse outcomes. Cardiac allografts with LVH have also been increasingly accepted as a viable way to expand the donor pool because of several studies demonstrating similar outcomes of ECD *vs.* SCD HT [150–153].

However, there remain conflicting data on whether HT using donor organs with both LVH and other comorbidities (e.g., hypertension and advanced age) has outcomes inferior to SCD HT [151–153]. It is important to consider the possibility that multiple high-risk characteristics or "hits" might eliminate any survival benefit from HT using those organs and donors with these risk factors should be approached with caution.

The reevaluation of organs considered to have "extended criteria" has widened the donor pool, although the survival benefit is often limited to specific subpopulations of waitlist candidates. These findings support the abandonment of historic, "strict" guidelines for which donor organs can be used with acceptable outcomes, particularly as both donor and recipient care continue to improve, and instead argue for a more nuanced approach to consideration of ECD donors.

Ethical Considerations

While novel strategies to increase the availability of donor organs show significant promise, they also carry ethical concerns (Table 2). In the utilization of DCD organs, death can only be pronounced when heart function is irreversibly lost, hence the "stand-off" period observed by DCD teams after asystole. However, all DCD HT involves the restarting of the previously "irreversibly dead" heart. Some authors have questioned whether this, by necessity, negates the previous determination of death as the patient may not meet death criteria from a biological systems perspective of irreversibility [14,154,155]. While a full exploration of these ethical questions is beyond the scope of this review, it has been suggested that modern techniques including *ex situ* heart perfusion and donor normothermic regional perfusion have assuaged legal concerns and created a more stable ethical framework for DCD HT [15]. In a 2018 review on the ethics of DCD by Rajab *et al.* [156], the authors argued that "reanimating" the donor heart after the declaration of circulatory death does not negate the fact that the organ was dead at the time of declaration. In addition, strategies like NRP by necessity create brain death in the donor, making the question of restarting the heart irrelevant. Finally, DCD is widely accepted in other organs, and the authors find no ethical rationale for rejecting the practice with heart donation [156].

Recently, the use of Hepatitis C and HIV positive organ donors has spurred ethical controversy and debate. In both cases, there are limited data on the potential interactions of DAA and HAART therapy with immunosuppressive agents used in transplantation [131,157]. Furthermore, there is also a lack of knowledge on the long-term outcomes of transplanted organs in these patients. In the United States, transplantation of HIV+ organs was banned in 1988, and HIV+ patients with end-stage organ failure have faced higher waitlist mortality and reduced transplant eligibility and access. Proponents of HIV+/D+ transplantation have balanced considerations of beneficence, in giving live-saving opportunities to HIV+ waitlisted patients, and non-maleficence, as there remain significant potential harms in transplanting HIV+ organs, including infecting recipients with new strains of HIV and the potential to accidentally spread the virus [131,158]. Ultimately, the fight for HIV+ transplantation in the United States culminated in

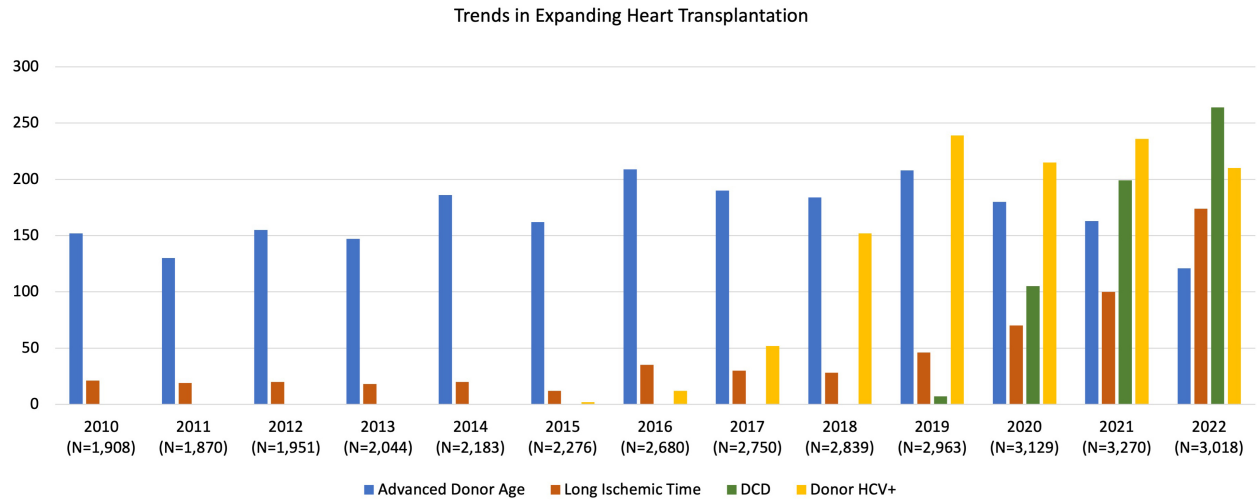

Fig. 4. Trends in expanding heart transplantation from 2010 to 2022. Data was obtained from UNOS database and includes all United States adult heart transplants since 2010 stratified into advanced donor age (>50 years, blue), extended ischemic times (>6 hours, orange), DCD (green), and HCV+ donors (based on nucleic acid amplification testing, yellow). Total heart transplants are listed within parentheses below each year.

the HIV Organ Policy Equity (HOPE) Act, signed into law in 2013, which reversed the ban on HIV+ transplantation under stringent conditions [131].

Finally, "extended donor-pool" hearts bring their own set of concerns, stemming in large part due to the extra risk assumed by the recipient in accepting an organ which would previously have been rejected. Donor organs with comorbidities including increased ischemic time, increased age, and potential infectious disease bring different risk calculations into play [135,159]. It is imperative for providers of organ transplants to apprise recipients of both the known and unknown risk of using extended or increased-risk grafts. If grafts with certain comorbidities are known to confer worse outcomes, is it ethical to transplant these organs, and if so, should recipients have the ability to decline a graft based on certain risk factors [159]?

Future Directions

As worldwide experience with expanded donor criteria grows, promising new avenues of scientific inquiry are being explored to optimize graft function. For DCD hearts, these include pharmacologic conditioning of the DCD heart as well as optimized support during the warm ischemic period [9,160–164]. Mitochondrial transplantation, erythropoietin with glycerin trinitrate and zoniporide, siRNA, and the use of mesenchymal stem cells are three interventions under active investigation which might protect the heart during its vulnerable ischemic period [160,161,163,164].

In infectious donor (HCV+/HIV+) transplantation, the new frontier is in recipient-donor mismatch [165]. While HCV D+/R– have been reported with excellent short-term outcomes thanks to DAA, HIV D+/R– transplants remain a potential realm to explore [159]. In South Africa in 2017, a life-saving partial living liver transplant was successfully performed using a graft from a HIV+ mother to her HIV– daughter. The transplant led to equivocal HIV transmission, with recipient seroconversion but no detectable HIV-1 RNA or DNA [166]. Because of the efficacy of HAART, there is also hope that undetectable viral HIV load may decrease the chances of transmission during organ transplantation. However, more studies are needed to understand the risk of transmission in organ transplant settings with D+/R– [167]. To date, we were unable to identify any HIV D+/R– heart transplants in the literature. However, if this advance became widespread it could be vital in areas of the world with high HIV prevalence, where a large proportion of potential deceased and living donors are HIV+, such as South Africa.

As the transplant community has begun to increasingly utilize expanded criteria donor hearts with good outcomes, there has been an effort to re-consider other contraindications to donation. There have been several case reports of transplants using donor hearts with significant valvular or congenital heart disease, with surgeons performing repairs on the back table and achieving acceptable short-term outcomes [168,169]. Another potential area of expansion is the use of COVID-19 positive donor organs. While initially deemed an absolute contraindication at the beginning of the pandemic, the continued transmission of the virus in many regions around the world has necessitated rethinking the use of these organs. This stance has been supported with a case series reporting on 5 successful COVID-19+ transplants without viral transmission to the recipient [168,170].

The search for viable donor organs to meet the growing demand has also spurred scientific inquiry outside of hu-

man grafts. As has been well-publicized, a team at the University of Maryland conducted the first heart transplant using a genetically-modified pig xenograft [171]. While further exploration of xenotransplantation is outside the scope of this review, the use of genetically-modified xenografts has exciting potential to bridge the donor gap, while also bringing with it a host of ethical and clinical concerns [172]. As demand grows for organ donation across the world, innovative new solutions, including xenotransplantation, three-dimensional (3D) bioprinting, and further reconsideration of human donors will continue to emerge.

Conclusion

Cardiac transplantation is the gold standard treatment for heart failure, but the number of transplants performed annually remains limited by the shortage of "acceptable" donor organs. In the last decade, several efforts have emerged to expand the donor pool (Fig. 4). While modern DCD HTs have been performed for over a decade, investigations into TA-NRP in the last 2 years have sparked renewed interest in DCD donors—particularly those considered marginal—and might increase the number of suitable DCD grafts. With the advent of DAAs, the number of HT from HCV+ donors have been increasing in the last several years, and these transplants have demonstrated comparable post-transplant outcomes to HT from HCV– donors. While Public Health Service Increased Risk Donors have become widely used with excellent post-transplant outcomes, the utilization of HIV+ donors is still in its infancy and has the potential to continue to expand the donor pool. Lastly, factors included within the "Extended Criteria Donors" designation, including increased ischemic time, offer new avenues of exploration for further expansion of the donor pool, but additional studies are needed to assess the safety of transplanting these grafts.

In summary, although significant strides have been made, there remains a discrepancy between the demand and supply of donor hearts. As practices continue to evolve to address this shortage, potential transplant candidates continue to die on the waitlist. As evidenced by the US experience (Fig. 4), donor grafts previously discarded have increasingly been used in the recent years, with over 700 expanded criteria donor hearts being used in 2022. However, there remains room for growth, both in the US and worldwide. Future efforts aimed at advancing donor graft preservation techniques and optimizing matching of marginal donor grafts with appropriate recipient populations may offer opportunities to further expand the pool of eligible donors.

Author Contributions

AK, JMR, and RTJ designed the research study. RTJ, MMS, and ELL performed the research. RTJ, MMS, ELL, and ALZ wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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